**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Applicant(s): Gleave, et al. | |
| Application No.: 10/646,391 | |
| Filed: 8/21/2003 | Group Art Unit: 1635 |
| Title: Treatment of Melanoma by Reduction in Clusterin Levels | Examiner: Amy Hudson Bowman |
| Attorney Docket No.: UBC.P-035 | |

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed 9/7/2005. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is The University of British Columbia.

Related Appeals and Interferences

Appeal No. 2005-2447 has been briefed and was argued orally on October 18, 2005 for commonly assigned application serial number 09/619,908. This Appeal relates to antisense with a different target, but includes arguments on the significance of method of treatment limitations in claims. To date, no decision has been received on this appeal.

Status of Claims

Claims 1-13 are pending in this application. Claims 1-10 are rejected and are the subject of this appeal. Claims 11-13 are withdrawn from consideration. In addition, the Examiner has

stated that claims 3, 6 and 9 are objected to because the sequences listed therein include sequences in addition to elected Seq. ID No. 4.[1]

Status of Amendments

No amendments to the claims after final rejection were made.

Summary of Claimed Subject Matter

This application relates to a method for treating melanoma in a mammalian subject by inhibition of clusterin, for example by administration of antisense oligonucleotides specific for clusterin. (Page 1, line 6-8). Clusterin itself is a known protein (Page 1, line 9 - Page 2, line 3; Page 3, lines 13 -17), with a known sequence. The human sequence is given by Seq. ID No. 1 . Antisense targeted to clusterin is also known in the art for treatment of prostate cancer, renal cell cancer and some prostate cancers, and for enhancement of the effects of chemotherapy agents and radiation. (Page 2, lines 4-9). Applicants' invention is based on the discovery that melanoma cell lines may express higher amounts of clusterin than normal melanocytes, and that reduction in clusterin expression results in an increase in apoptotic cell death of melanoma cells. (Pages 8 and 9 and Figures).

Grounds of Rejection to be reviewed on Appeal

1. Claims 1-5 stand rejected under 35 USC § 112, second paragraph, for lack of enablement.

2. Claims 1-5 stand rejected as anticipated by Monia.at al (US 2004/0053874). Claims 1-5 and 9-10 stand rejected as anticipated by Gleave et al (WO/49937) or Gleavse et al. (US 2002/012822).

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[1] It is unclear why the Examiner refers to claim 3 as an improper Markush group, since it does not contain a Markush group listing of alternatives.

3. Claims 1-10 stand rejected as obvious over Gleave et al. (WO 00/49937) in view of Barracchini (US 5,801,154).

4. Claims 1, 2, 9 and 10 stand provisionally rejected for obviousness-type double patenting in view of claim 1-3 of co-ending application no. 10/828,394.

Argument

1. The Enablement Rejection

Rejected claims 1-5 relate to a method of treatment of melanoma by reduction of clusterin generally (Claim 1), or using an unspecified antisense oligonucleotide (claims 2-5). In contrast, claims 6-10 which are not subject to this rejection recite specific antisense sequences disclosed in the application. The Examiner argues that while the claims are enabled for Seq. ID No. 4 there is no enablement for antisense generally or for other therapeutic agents.

Applicants respectfully submit that this rejection should be considered in three parts:

(a) enablement of other enumerated antisense species, even though the Examiner asserts that these sequences within the scope of claims 6 and 9 are improper Markush groups.

(b) enablement of antisense generally, as defined in claims 2-5.

(c) enablement of therapeutic agents not limited to antisense.

These three parts are argued separately below.

In presenting an enablement rejection, the burden is on the Examiner to present reasons why a person skilled in the art would be unable to practice the claimed invention without undue experimentation. *In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982). In this case, the Examiner has made generalized arguments with respect to the alleged "unpredictability of *in vivo* delivery of the therapeutic agent," and has cited some review articles not specific to clusterin in support of this argument. Applicants have responded with the Declaration Under Rule 132 concerning some preliminary human clinical trials for Seq. ID No. 4 (Attached in Evidence Appendix). The Examiner acknowledges that this declaration is sufficient to prove enablement

as to Seq. ID No. 4, but argues that it does not do so for other sequences or antisense generally. Applicants respectfully submit that the Examiner has improperly looked only at the number of antisense compounds tested, without revisiting the question of enablement and of whether this evidence rebuts, as a scientific matter, the general argument of unpredictability on which the enablement rejection is based. Stated differently, the Examiner has failed to assess whether the evidence in the record, taken as a whole, is sufficient to say that one reasonably skilled in the art could not make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987).

In the Official Action, of April 8, 2005, the Examiner cites a variety of general difficulties that have been said to confront antisense technology. Applicants respectfully submit, however, that these are not sufficient to maintain the enablement rejection given the facts of record in this case.

The Examiner cites Branch for a teaching that "because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be found by empirically screening a large number of candidates for their ability to act inside cells." Branch relates to the ability to predict, from the sequence alone, which complementary antisense species will work as antisense in a cell. In the present case, however, specific oligonucleotide antisense sequences that are effective to inhibit clusterin expression are disclosed and indeed are known from the art. Since the accessability of the RNA is a function of the RNA being in a cell, and not dependent on whether that cell is *in vitro* or part of an organism, this teaching of Branch casts no doubt on and has no relevance to the enablement of the present invention.

The Examiner cites Green et al. for a variety of statements critical of the state of development of antisense technology. These statements are very general, and merely identify issues such as toxicity that may pose obstacles. These obstacles should be dealt with by the Food and Drug Administration, and should not create a justification to require human clinical data for

multiple examples in order to meet the enablement requirement of the patent statute. Furthermore, Applicants have shown through their declaration, that at least one antisense within the scope of the claims, Seq. ID No 4, does not experience significant difficulties with toxicity. Not all embodiments of an invention need to work equally well in order for there to be enablement.

The Examiner cites the Jen et al. article as stating that "one of the major limitations for the therapeutic use of AS-ODNS .. is the problem of delivery .. presently some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable." The overall tone of the article is far less negative that this excerpt would suggest. For example, several approaches for delivery are described in the article on Pages 313-314, and the cited passage (Page 313) does not appear to apply to all of them. Furthermore, the declaration evidence shows that naked antisense of Seq. ID No. 4 when administered to humans is active in cells of different cancer types that overexpress clusterin to reduce clusterin expression without any special delivery or targeting vehicle.

The Examiner also argues that the claims lack enablement because there is no specific teaching of how to administer the therapeutic agent. In this regard, the Examiner cites a reference to Crooke et al. for a teaching that "extrapolation from in vitro uptake studies to in vivo pharmacokinetic behavior are entirely inappropriate." The Examiner has offered no reasoning, however, why anyone would consider in vivo pharmacokinetic studies to determine appropriate dosages and administration timing to constitute undue experimentation. Such studies are a routine part of new drug development, and take into account balancing of efficacy and toxicity. (See Specification, Page 5, lines 1-5).

(a) *enablement of other enumerated antisense species*

Claim 6 sets forth a list a list of specific sequence numbers, namely sequence ID Nos. 2-19. Although claim 6 is not rejected, the Examiner has considered this claim only to the extent of the elected Seq. ID No. 4. It is noted, however, that these are specific sequences said in the

specification to be operative and that the Examiner has offered no reasoning that would lead a person skilled in the art to view these sequences as requiring different enablement from sequence ID No. 4.

Furthermore, the Examiner' assertion that claims 6 and 9 contain an improper Markush group is inconsistent with applicable guidelines. As noted in the MPEP, § 803.02

> when the Markush group occurs in a claim reciting a process or a combination (not a single compound), it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship, and it is clear from their very nature or from the prior art that all of them possess this property.

The claims here at issue are method claims, and all of the members of the Markush listing (Seq. ID Nos. 2 to 9) share the common property of complementarity and antisense activity with respect to expression of human clusterin.

(b) *enablement of antisense generally*

Applicants submit that claims 2-5, which are related to antisense therapeutic agents without recitation of specific sequences are also enabled. Numerous antisense agents are known in the art that inhibit expression of clusterin, and a variety of these are specifically recited in the specification. Thus, the issue raised by the Examiner is not a teaching of a sufficient number of species of antisense, but rather an assertion that these other known sequences cannot be predicted to work. As demonstrated above, however, the Examiner's evidence of the state of the art is overly general, and has not been considered in the light of the facts of record that relate to Applicants specific invention.

(c) *enablement of therapeutic agents not limited to antisense*

Claim 1 is directed to a method of treatment of melanoma in which the therapeutic agent is not limited to antisense. In the advisory action, mailed November 10, 2005, the Examiner states that the enablement of the one specific oligo (Seq. ID No. 4) of the declaration, does not

enable any type of therapeutic. While this is the first time this argument was made, Applicants understand this as a separate basis for the rejection of claim 1.

In this regard, Applicants submit that enablement is only required as of the date of the application. Applicants disclosed in the specification the two types of agents of which they had knowledge of specific operative compounds, namely antisense and RNAi. It is not relevant that Applicants have not listed or otherwise enabled compounds (such as small molecule inhibitor of clusterin) that were not known as of the filing date of the application, because such compounds are **not** the claimed invention. Rather, the claimed invention, the thing that must be enabled as of the filing date, is a method of treating melanoma by inhibition of clusterin expression. This is Applicants' contribution to the art and claims should be granted that dominate future ways of practicing the method so as to give Applicants the benefit of this contribution.

2. Anticipation Rejections

The claims of this application are all directed to a method of treating melanoma using agents that inhibit clusterin expression. Since agents that inhibit clusterin expression are known from the art, and were used in a therapeutic application other than melanoma, the claims of this application are of the type that is sometimes referred to as "second medical use" claims. As discussed separately below, however, each of the anticipation rejections is based on the proposition that the statement of intended use, i.e., treatment of melanoma, may be ignored, and that anticipation is found in a reference that teaches administration of an inhibitor of clusterin expression for an entirely different purpose, and to patients who are not identified as having melanoma. Applicants submit that this is unfounded both in law and as a matter of public policy.

In support of the rejection, the Examiner cites MPEP § 2112 for a teaching that "something that is old does not become patentable upon the discovery of a new property." However, Applicants are not trying to claim compositions for inhibition of clusterin expression based upon the discovery of a new property. They are claiming a method that is based upon the newly discovered property. The same section of the MPEP that is cited by the Examiner states

that "the discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using." *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957).

The Examiner also argues that the reference to melanoma is a mere statement of intended use, entitled to no patentable weight, because the only actual method step, i.e., administering, is the same. Thus, in the Advisory Action of November 10, 2005, the Examiner states that "the intended use of treating melanoma does not recite any essential structure or step." Applicants disagree. The treatment is given to a subject, and the fact that the treatment is for melanoma recites an essential characteristic of the subject being treated, they have been diagnosed with melanoma.

Of relevance to this issue are several recent cases from the Court of Appeals for the Federal Circuit. The claims of the present application recite "a method for treatment of melanoma in a mammalian subject." The Court of Appeals for the Federal Circuit has recently observed that

> In general, a preamble limits the [claimed] invention if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808, 62 USPQ2d 1781, 1784 (Fed. Cir. 2002) (quoting *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999)). "[A] claim preamble has the import that the claim as a whole suggests for it. In other words, when the claim drafter chooses to use both the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects." *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620, 34 USPQ2d 1816, 1820 (Fed. Cir. 1995).

*Eaton Corp. v. Rockwell International Corp.*, 66 USPQ2d 1271 (Fed. Cir. 2003). In the present case, the preamble cannot be deemed superfluous, since it says what is being accomplished by the method, namely a treatment of melanoma, and the claim without these words is meaningless.

Indeed, the notion that preamble language is generally meaningless in method claims would render second use method claims impossible.

The importance of the preamble in method claims of this type is reflected in *Jansen v. Rexall Sundown, Inc,* 68 USPQ 2d 1154 (Fed. Cir. 2003). In that case, the claims at issue were directed to "a method of treating or preventing macrocytic-megaloblastic anemia" by administration of a composition of defined components "to a human in need thereof." The accused product was a dietary supplement having a composition as defined in the claims. It was labeled for uses that did not include treating or preventing macrocytic-megaloblastic anemia. The Federal Circuit found that the claims were limited to the use, as stated in the preamble. Similarly, in *Rapoport v. Dement*, 59 USPQ2d 1215 (Fed. Cir. 2001) a claims directed to "a method for treatment of sleep apneas" was interpreted as being just that, and not a method for treating symptoms associated with sleep apneas, which was found in the art.

In *Jansen* the Federal Circuit observed that

> in both *Rapoport* and this case, the claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.' In both cases, the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose. The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method is performed.

*Jansen* at 1158. In this case, the claim is directed to "a method for treating melanoma in a mammalian subject." Treatment is given to "the subject" and is "effective to reduce the effective amount of clusterin in the melanoma cells." Since there cannot be melanoma cells in a subject

unless they have melanoma, this recitation is equivalent to the "in need" statements of *Jansen* and *Rapoport*.[2]

In *Merck & Co. Inc. v. Teva Pharmaceuticals USA Inc.*, 68 USPQ2d 1857 (CA FC 2003) a claim to a method of treating a specified condition comprising administering an old compound to a person in need of treatment was found valid over, and not anticipated a prior reference saying the old compound could be used in pharmaceuticals generally because it did not disclose every limitation of the claimed invention.

Applicants further note an earlier case involving a claim to a second medical use. In *In re Marshall*, 198 USPQ 344 (CCPA 1978), the invention dealt with the new pharmaceutical use (weight loss) for a previously known drug which was described in the Physician's Desk reference (PDR). The CCPA reversed the holding of anticipation observing that "if anyone ever lost weight by following the PDR teachings it was an unrecognized accident. An accident or unwitting anticipation of an invention cannot constitute an anticipation." 198 USPQ at 346.

As discussed below, none of the art cited as anticipatory in this case says anything about melanoma or treatment of melanoma by inhibition of clusterin expression . Thus, these references do not teach each and every limitation of the claimed invention and the rejections are therefore improper and should be reversed.

a. *US 2004/0053874 of Monia et al*

The Examiner argues that Monia et al. "teach a method of treating an animal having a disease or condition associated with clusterin comprising administering a therapeutically effective amount of an antisense compound targeted to a nucleic acid encoding clusterin, wherein

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[2] It is assumed that the Examiner has not compelled an Appeal of this issue in this case merely because of a semantic issue over the form of recitation that indicates that the subject is "in need of treatment for melanoma" since Examiners are directed to suggest amendments that would overcome the rejection, and no suggestion of such an amendment has been made here. MPEP § 707.07(i) II.

said compound inhibits expression of clusterin." The Examiner does not point to any teaching concerning melanoma, but instead says that such a teaching is not necessary because the method step (administering) is the same (Office Action of September 7, 2005). Based on the law as set forth above, Applicants submit that this argument is in error.

b. *WO 00/49937 of Gleave at al*

The Examiner argues that Gleave '937 "teach a method of treating cancer in a mammalian subject comprising the administration of an antisense oligonucleotide effective to inhibit TRPM-2 (another name for clusterin) in tumor cells." The Examiner does not point to any teaching concerning melanoma, but instead says that such a teaching is not necessary because the method step (administering) is the same (Office Action of September 7, 2005). Based on the law as set forth above, Applicants submit that this argument is in error.

c. *US 2002/0128220 of Gleave et al.*

The Examiner argues that Gleave '220 "teach a method of treating cancer in a mammalian subject comprising the administration of an antisense oligonucleotide effective to inhibit TRPM-2 (another name for clusterin) in tumor cells." The Examiner does not point to any teaching concerning melanoma, but instead says that such a teaching is not necessary because the method step (administering) is the same (Office Action of September 7, 2005). Based on the law as set forth above, Applicants submit that this argument is in error.

3. Obviousness Rejection

Claims 1-10 stand rejected under 35 USC § 103 as obvious over the combination of Gleave et al. WO/49937 in combination with US Patent No. 5,801,154 of Baracchini. In this rejection, the Examiner continues to rely on the argument that the statement of intended use of the method, treatment of melanoma, is irrelevant, and that Gleave et al therefore meets every limitation except modifications to the backbone of the antisense as recited in claims 4-7.

Baracchini discloses backbone modifications generally, but has no specific relevance to clusterin antisense. Moreover, Baracchini does nothing to overcome the fundamental deficiency of the primary reference, namely the absence of any disclosure with respect to a relationship between melanoma and clusterin expression. This being the case, the references fail to suggest the claimed invention and the rejection should be reversed.

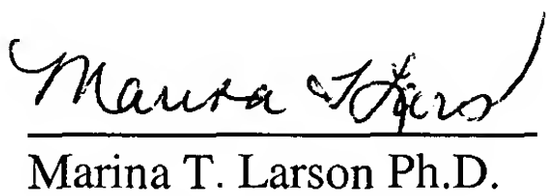
4. Double Patenting Rejection

Claims 1, 2, 9 and 10 stand provisionally rejected for obviousness-type double patenting over claims 1-3 of US Application Serial No. 10/828,394. These claims are directed to the treatment of cancerous angiogenesis-related diseases using antisense targeting clusterin. Neither the claims nor the '394 application mention melanoma. The examiner has not established that melanoma is a cancerous angiogenesis-related disease, and therefore has not established that there is any overlap in the claims. The rejection is maintained, however, because the treatment of melanoma is allegedly a mere statement of intended use that is of no patentable weight. Thus, this rejection depends on the same erroneous interpretation of the claim scope as the anticipation and obviousness rejections, and should be reversed for the same reasons.

5. Conclusion

For the foregoing reasons, Applicants submit that all of the rejections in this case should be reversed and that claims 1-10 of this application are allowable. The case should therefore be returned to the Examiner for consideration of the non-elected species.

Respectfully submitted,



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## Claims Appendix

1. A method for treatment of melanoma in a mammalian subject, comprising the step of administering to the subject a therapeutic agent effective to reduce the effective amount of clusterin in the melanoma cells.

2. The method of claim 1, wherein the therapeutic agent is an antisense oligodeoxynucleotide effective to reduce the effective amount of clusterin in the melanoma cells.

3. The method of claim 2, wherein the antisense oligodeoxynucleotide spans either the translation initiation site or the termination site.

4. The method of claim 3, wherein the antisense oligodeoxynucleotide is modified to enhance in vivo stability relative to an unmodified oligodeoxynucleotide of the same sequence.

5. The method of claim 4, wherein the modification is a 2'-O-(2-methoxyethyl) modification.

6. The method of claim 5, wherein the antisense oligodeoxynucleotide consists essentially of an oligodeoxynucleotide selected from the group consisting of Seq. ID. Nos. 2 to 19.

7. The method of claim 6, wherein the antisense oligodeoxynucleotide consists essentially of an oligodeoxynucleotide consisting of Seq. ID. No. 4.

8. The method of claim 7, wherein the oligonucleotide has a phosphorothioate backbone throughout, the sugar moieties of nucleotides 1-4 and 18-21, the "wings", bear 2'-O-methoxyethyl modifications and the remaining nucleotides are 2'-deoxynucleotides.

9. The method of claim 2, wherein the antisense oligodeoxynucleotide consists essentially of an oligodeoxynucleotide selected from the group consisting of Seq. ID. Nos. 2 to 19.

10. The method of claim 9, wherein the antisense oligodeoxynucleotide consists essentially of an oligodeoxynucleotide consisting of Seq. ID. No. 4.

## Evidence Appendix

## Declaration Under Rule 132

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant(s): Gleave, et al.<br>Application No.: ~~09/967,726~~ copy filed in 10/646,391<br>Filed: 9/28/2001<br>Title: Chemo-and Radiation-sensitization of Cancer by Antisense TRPM-2 Oligodeoxynucleotides<br>Attorney Docket No.: UBC.P-022<br>Customer No.: 021121 | Group Art Unit: 1635<br>Examiner: Tracy Ann Vivlemore<br>Confirmation No: 6881 |

Commissioner for Patents

PO Box 1450

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DECLARATION UNDER RULE 132

The undersigned each hereby declare as follows:

1. I am a named inventor of the above-captioned application. As such, I am familiar with the application, including the claims.

2. This declaration is submitted to set forth results from clinical trials that have been conducted since the filing of the application.

3. This declaration is signed by less than all of the inventors, because the other inventors, H. Miyake and T Zellweger, are no longer associated with the project, and have had no involvement, and thus no personal knowledge of the trials reported here.

4. Limited clinical testing (two Phase I studies) has been conducted to evaluate toxicity of OGX-011, an antisense oligonucleotide that has the sequence as set forth in Seq. ID NO.: 4 of the above-captioned application. The oligonucleotide is modified as described in Application Serial No. 10/080,794. A total of 25 patients with localized prostate cancer with high risk features were enrolled in the first study. In the second study, a total of 30 patients suffering from renal cancer, non-small cell lung cancer, ovarian cancer, peritoneal cancer or prostate cancer were enrolled, each of whom was refractory to one or more prior treatment regimens.

5. In both phase I studies, antisense treatments were made at levels of 40, 80, 160, 320, 480 or 640 mg and administered intravenously 3 times during the first week, and once a week thereafter. In the first phase I study, antisense therapy was combined with concurrent hormone ablation therapy for 5 weeks prior to radical prostatectomy. Concentrations of OGX-011 in prostate tissue and of TRPM-2 mRNA and protein in prostate and lymph node tissue were determined. At all levels of antisense, dose-dependent reduction in levels of TRPM-2 mRNA was observed in the lymph nodes of the patients treated, and in laser captured, micro-dissected prostate cancer levels, indicating that all of the amounts of antisense tested had a measurable affect at the expression level. The amount of TRPM-2 in serum also decreased in a dose-dependent manner.

6. This study established a dose of 640 mg as the recommended dose based on safety, tolerability, and tissue levels of antisense and TRPM-2 mRNA and/or protein.

7. In the second Phase I study, two schedules of concurrent docetaxel treatment were evaluated: 30 mg/m$^2$ weekly or 75 mg/m$^2$ every three weeks. Of 18 patients with measurable disease, the interim response rate (the study is still in progress) was 38.9%, including 33.3% with stable disease, and 5.6% achieving an objective partial response.

8. Two ovarian cancer patients showed reductions in the measured amount of the tumor marker CA125. In one patient receiving 160 mg OGX-011, the amount of CA125 marker decreased from 19,600 to 4720 over 71 days after commencement of treatment. In another who received 480 mg OGX-011, the marker level decreased from 2000 before treatment to around five hundred after 33-44 days. A slight increase to around 900 was observed during a second treatment cycle. Other patients with ovarian cancer had low initial CA125 and so a decrease could not be evaluated.

9. Two prostate cancer patients showed reduction in the amount of PSA tumor marker. In one patient receiving 40 mg OGX-011, the PSA level decreased from 90 prior to therapy to 35 after 4 treatment cycles at approximately 45 day intervals, and remained at 56 at a later date. In a second patient receiving 320 mg OGX-011, the PSA level dropped from a pre-treatment level of 1478 to a level of about 425 after 4 cycles of treatment.

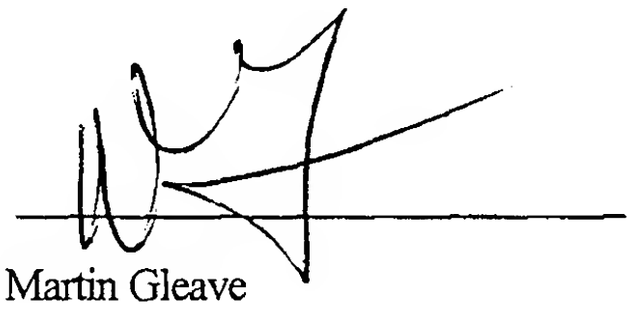
10. The selection of initial dosages for this study was consistent with standard protocols for clinical trials to evaluate toxicity, and no experimentation was needed to arrive at dosage levels that produced observable reduction in TRPM-2 mRNA or serum TRPM-2.

11. While the data in this study is preliminary and difficult to draw many conclusions from because of the small sample size, the number of variables that were considered, including prior treatment of the patients, and the short duration of the test, several conclusions can be drawn. Standard

protocols for trial design were used and arrived, without experimentation, at working levels for antisense dosing that produced reduction in TRPM-2 mRNA and serum TRPM-2 without significant toxicity, and this treatment in combination with docetaxel produced beneficial results in patients who had been refractory to prior treatment.

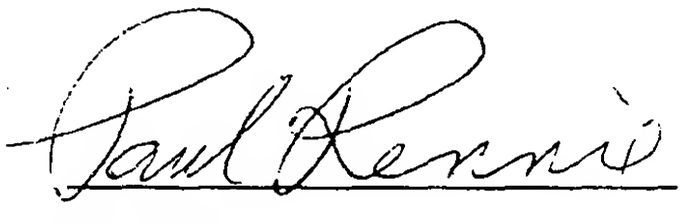
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

dated: April 6/05



Martin Gleave

dated: April 5/05



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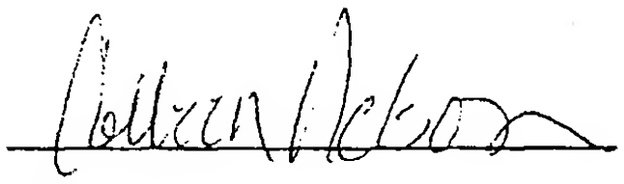

Colleen Nelson

## Related Proceedings Appendix

None